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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,877	01/23/2001	Kenneth S. Polonsky	ARCD:307USD1	4378

7590 10/16/2002
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EXAMINER

RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 10/16/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicant(s)

09/768,877

Applicant(s)

POLONSKY ET AL.

Examiner

Delia M. Ramirez

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 July 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-21 and 49-113 is/are pending in the application.
- 4a) Of the above claim(s) 65-113 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-21, 49-52, 54-64 is/are rejected.
- 7) ☒ Claim(s) 53 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 January 2001 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Status of the Application

Claims 19-21, 49-113 are pending.

Applicant's election without traverse of Group I, claims 18-21 and 49-64, drawn to a method of screening for a modulator of calpain function, in Paper No. 11, filed on 4/16/2002 is acknowledged.

A supplemental restriction requiring the election of one polypeptide sequence was mailed in Paper No. 12 on 6/18/2002. Applicant's election with traverse of SEQ ID NO: 2 in Paper No. 13, filed on 7/24/2002 is acknowledged.

Applicant's traverse is on the ground(s) that it would not be unduly to search for all 9 polypeptide sequences since the polypeptides are alternative splicing products of the same gene and they have considerable overlap and identity with one another. Furthermore, Applicants argue that US Patent No. 6235481 has claims directed to the same 9 polypeptides, therefore a search of all these polypeptides would not be a burden on the Office since the polypeptides were determined to be novel by the PTO.

Applicant's arguments have been fully considered but are not deemed persuasive to withdraw the supplemental restriction requirement. The claims in US Patent No. 6235481 are directed to polynucleotides and not polypeptides. A search for polynucleotides, which are structurally and chemically different from polypeptides, is not co-extensive to polypeptides. While the polypeptides are alternative splicing products of the same gene, they have different sequence and structure, therefore a sequence search of one polypeptide is not co-extensive to another polypeptide. The instant application is directed to a method of use of polypeptides,

Art Unit: 1652

which would require a sequence search of each polypeptides, a class/subclass search, as well as patented and non-patented literature searches in order to be comprehensive. In addition, it is application No. 09/768877 which is being currently examined and not application No. 09/422869 (now US Patent No. 6235481). Thus, for the reasons indicated above, a search of a method of use for all nine polypeptides would impose an undue burden on the Office.

The requirement is deemed proper and therefore is made FINAL.

Claims 65-113 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

1. The use of trademarks has been noted throughout this application. See, for example, "Clonetech" in page 124. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Priority

2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/105052 filed on 10/21/1998 and 60/134175 filed on 5/13/1999.

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/422869 filed on 10/21/1999.

Information Disclosure Statement

4. It is noted that according to PTO records, an IDS was filed on 3/26/2001, however no PTO form 1449 or copies of the references cited can be found in the application. Applicants are requested to submit a copy of such IDS in response to this Office Action if consideration of such IDS is desired.

5. A listing of references appears in the specification. Applicant is reminded that a listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

6. The drawings have been reviewed and are objected under 37 CFR 1.84 or 1.152. See attached Notice of Draftsperson's Patent Drawing Review. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite the processing of the application.

Claim Objections

7. Claim 53 is objected to because it is directed to a method of use of a non-elected invention. It is suggested that the claim be amended to recite only SEQ ID NO: 2, which is the polypeptide elected. For examination purposes, the claim has been interpreted as directed to the method of claim 52 wherein the calpain 10 polypeptide has an amino acid sequence as set forth in SEQ ID NO: 2. Appropriate correction is required.

8. Claims 50 and 56 are objected to because of the recitation of "Suc-Leu-Tyr-AMC". Abbreviations unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. It is suggested that the term "N-succinyl(Suc)-Leu-Tyr-amidomethylcoumarin (AMC) be used once. Appropriate correction is required.

9. Claims 49 and 55 are objected to for the following reasons: for clarity, it is suggested that the claims be amended by adding the term "in the absence of said modulator". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 18-21, 49-50, 54, 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit: 1652

12. Claims 18-21 and 49-50 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 18 is drawn to a method of screening for a modulator of a polypeptide, however no step is disclosed for correlating a change in the standard activity profile and the presence of a modulator. It is suggested that the claim be amended to recite “assaying for a change in the standard activity profile, wherein a change in the standard activity profile is an indication of the presence of a modulator” or similar. For examination purposes, the suggested language indicated above has been used in the interpretation of the claim. Correction is required.

13. Claims 18, 54, and 57 (claims 19-21 dependent thereon) are indefinite in the recitation of “standard activity profile” as it is unclear absent a statement defining the term. An enzyme activity profile will be different depending on the conditions chosen to measure such activity (i.e. substrate, temperature, pH, etc.). It is suggested that if the term refers to determining the calpain polypeptide activity against a specific substrate in the absence of a modulator, it is suggested that the term be defined in the claims by adding language such as “wherein said standard activity profile is determined by measuring the activity (or binding) of the calpain polypeptide to ? (substrate) in the absence of the modulator” or similar. For examination purposes, the suggested language indicated above has been used in the interpretation of the claim. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

Art Unit: 1652

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 18-21, 49-52, 54-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 18-21, 49-52 and 54-64 are directed to a method of screening for a modulator of calpain wherein a genus of calpain polypeptides are used. While the specification has disclosed the human calpain 10 polypeptides of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16 and 18, no disclosure of the structure of other calpain polypeptides as encompassed by the claims has been provided which would allow one of skill in the art to practice the full scope of the claimed method. No disclosure of the critical structural elements a polypeptide should have to display calpain activity has been provided either.

While one can argue that other calpain polypeptides can be isolated by sequence comparison with a known protein of known function, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork (Genome Research, 10:348-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a

Art Unit: 1652

desaturase. There are many types of calpain polypeptides in humans and other species which are encompassed within the scope of the claimed method. The specification only discloses a few species of the genus of polypeptides required to practice the claimed method which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of the claimed method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

16. Claims 18-21, 49-52, 54-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for inhibitors of the human calpain polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for a method of screening for inhibitors of any calpain polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims.

The scope of the claims is not commensurate with the enablement provided in regard to the large number of unknown calpain polypeptides from any source required to practice the claimed method. As indicated previously, the specification discloses the structure of 9 calpain 10 polypeptides. The state of the art teaches that the isolation of other polypeptides of similar

Art Unit: 1652

function is unpredictable based on sequence homology. See the teachings of Bork (Genome Research, 10:348-400, 2000), Broun et al. (Science 282:1315-1317, 1998) and Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) already discussed. Since the amino acid sequence determines the function of a polypeptide, one would require some knowledge and/or guidance as to how structure relates to function to isolate polypeptides of calpain activity and practice the claimed method. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to maintain the desired function, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to screen and isolate those polypeptides, as encompassed by the claim, with calpain activity, to practice the claimed method. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 18, 20-21, 51, 54, 58-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyer et al. (Biochem. J. 314:511-519, 1996). Meyer et al. teaches the cloning, expression and characterization of human calpain I using the baculovirus expression system. Meyer et al. teaches the characterization of the recombinant human calpain I by testing different inhibitors of calpain activity. The method for screening inhibitors (modulators) of calpain I taught by Meyer et al. requires (1) combining the recombinant calpain with a substrate (succinyl(Suc)-Leu-Tyr-

Art Unit: 1652

methoxynaphthylamine(MNA), (2) measuring the activity of the recombinant calpain against the substrate in the absence of the inhibitor, (3) measuring the activity of the recombinant calpain against the substrate in the presence of the inhibitor and (4) determining the change in activity by comparison of the activity in the absence and presence of the inhibitor (page 513, column 1-page 514, column2). The recombinant calpain is recombinantly expressed in insect cells. Claims 18, 20-21, 51, 54, and 58 are drawn to a method of screening for modulators of calpain activity (function) wherein a calpain polypeptide obtained by any method or made recombinantly, is contacted with a substrate in the absence and presence of a modulator, the activity is measured in the presence and absence of the modulator and a change in activity is correlated with the presence of a modulator. Claims 59-60 are drawn to the method described above wherein the calpain polypeptide is obtained by isolating a cell containing said polypeptide. Since the recombinant calpain of Meyer et al. is expressed in insect cells (page 513, column 1, Production and purification of rhcalpain I), the recombinant calpain is contained by a cell. Therefore, the teachings of Meyer et al. anticipates the claims as written.

Allowable Subject Matter

18. Claim 53 appears to be allowable over the prior art of record.
19. Claim 53 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Art Unit: 1652

Conclusion

20. No claim is in condition for allowance.

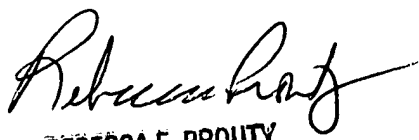
21. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

22. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652


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